IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	Group Art Unit: **1644**
Fick *et al.*	Examiner: **Michael Szperka**
Serial No.: **10/826,797**	Confirmation No: **1468**
Filed: **April 16, 2004**	Customer No: 09157
Title: **METHOD FOR TREATMENT OF ALLERGIC ASTHMA**	**CERTIFICATE OF ELECTRONIC FILING** I hereby certify that this correspondence is being electronically filed with the Commissioner for Patents, on July 26, 2006: BY: Christine Ricks

DECLARATION OF YAMO DENIZ, PH.D. UNDER 37 C.F.R. § 1.132

Sir:

I, Yamo Deniz, M.D., FAAAAI, declare and say as follows:

1. I am a Senior Medical Director and Senior Clinical Scientist at Genentech, Inc., South San Francisco, CA 94080.

2. I have extensive expertise in the area of clinical asthma. I am also very familiar with the initial controversy and conflicting hypotheses surrounding the initial clinical efficacy of anti-IgE therapeutics in the treatment of asthma, specifically, the connection between late asthmatic response ("LAR") and IgE. Attached is my Curriculum Vitae indicating my education, publications, positions of responsibility in the field.

3. I am aware that the claims in the above captioned patent application have been rejected for being obvious over Larsen *et al.*, specifically because Larsen *et al.* is alleged to disclose that LAR is an IgE-mediated disorder

4. I am familiar with the disclosure of Larsen *et al.* Specifically, I understand that Larsen *et al.* purports to have described an animal model for late asthmatic responses. Moreover, this animal model involved immunizing New Zealand white rabbits within the first 24 hours of birth, which resulted in the production of homocytotropic antibody (*i.e.*, IgE). Serum from these animals was then injected into naïve animals in a process known as "passive immunity." As a result of observation of this model, the authors concluded that: "[L]ate asthmatic response can be passively transferred, the response is dependent on the presence of antigen-specific IgE, and the response is blocked in a dose-dependent manner by the presence of antigen-specific IgG." *Larsen et al.* at 253.

5. It is my considered scientific opinion that data resulting from the Larsen *et al.* animal model of passive immunity in rabbits is insufficient to establish that LAR is an IgE-mediated disorder in humans. I base this opinion on the following: (1) passive immunity is generally an inadequate model of the process of active immunity; (2) regardless of the relevance of passive immune animals in modeling active asthma reactions, the specific passive immune as proposed by Larsen *et al.* lacks sufficient scientific controls to be probative; and (3) mammalian immunology, especially that between rabbits and humans, is sufficiently distinct that the conclusions based on study of rabbit late phase reactions do not conclusively correlate with human late phase reactions, especially late phase asthma.

6. Continuing, one significant weakness of the passive immune model recited in Larsen *et al.* is actually alluded to in the discussion following the body of the article. Specifically, in the discussion that follows (*e.g.*, page 261), Dr. Larsen is asked how is sure that IgE is in fact responsible for LAR, and whether or not he has purified the IgE from the serum. In response, Dr. Larsen replies such an experiment would conclusively prove IgE is responsible for LAR, but

that he in fact has not yet done this experiment. His response to the question that IgE was in fact responsible for LAR, was that heat was observed to inactive the response. In my opinion, which would be corroborated by one of even minimal skill in the art, is that such a heat in activation experiment only proves that the active ingredient can be inactivated (similar to what one would expect from other proteins), not that it is in fact, IgE. The fact that the active ingredient in the serum share a property (*i.e.*, heat activation) common to most, if not all proteins, is hardly indicative of the precise identity.

7. Continuing further, another weakness of the Larsen passive rabbit model is the reliance upon passive cutaneous anaphylaxis (PCA) as a marker for IgE. While this test is suggestive of the presence of IgE, it does not rule out the possibility that the LAR effect is caused by something else in the serum. The serum alleged to contain IgE is derived from rabbits based on the time-course exposure to allergen, not on any quantitative analysis of the presence of actual immunoglobulin. The failure of Larsen *et al.* to provide a control serum devoid of IgE (even admittedly so), is a missing critical link in any scientific endeavor to prove that this particular component of serum is responsible for the observed effect.

8. Finally, the postscript discussion further illustrates the weakness of the model is establishing a correlation between this model and late asthmatic reactions in humans. On page 262, a reviewer remarks that "short challenges with high concentrations are rather artificial" and that a prolonged, low level exposure over a longer period of time would be more appropriate to measure. Additionally, as a result of the cross-species variability in the etiology of asthma in mammals, one is not able to predict that an understanding of reactions associated with this disease in certain other mammals is indicative of how similar reactions are controlled in humans. For example, the reference Tepper *et al.*, "The Role of Mast Cells and IgE in Murine Asthma," referenced in the accompanying patent application and cited of record as document #304

discloses that neither mast cells nor IgE greatly influence anaphylaxis, airway hyperreactivity or airway inflammation in a murine asthma model. As a result, it is difficult, if not impossible to extrapolate meaningful conclusions regarding the pathology of human asthma from animal models of lower mammals such as rabbits and mice.

9. As a result, the Larsen *et al.* animal model is insufficient to support a conclusion that LAR is an IgE-mediated reaction in humans.

10. I hereby declare that all statements made herein are of my own knowledge, are true, and that all statements made on information or belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

Signed: Yamo M. Deniz, MD

Yamo Deniz, M.D., FAAAAI

Date: 7/25/06

CURRICULUM VITAE

YAMO DENIZ, MD, FAAAAI

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EDUCATION:

Undergraduate	B.A. (Chemistry)	College of the Holy Cross, Worcester, MA	1987
Graduate or Professional	M.D.	University of Massachusetts Medical School, Worcester, MA	1994

POSTGRADUATE TRAINING:

Pediatrics Internship	Long Island Jewish Medical Center,	7/94-6/95
Residency	New Hyde Park, NY	7/95-6/97
Pediatric Allergy & Immunology	Duke University Medical Center, Durham, NC	7/97-6/99
Clinical Fellowship		7/99-11/99
Research Fellowship		

ACADEMIC CAREER:

Hospital Appointment	Karolinska Institute Hospital, Stockholm, Sweden	12/99-6/01

PROFESSSIONAL CAREER

Chair, Xolair Development Strategy Team	Genentech	2001-2006
Sr. Clinical Scientist/ Medical Director	Genentech	2001-present
Chair, Xolair Global Medical Strategy Team	Genentech	2002-2006
Xolair, Clinical BLA Filing Team	Genentech	2001-2003
Xolair, PADAC preparation Team	Genentech	2001-2003
Anti IgE Development Team Leader	Genentech	2003-present
Anti OX 40L Early Development Project Team leader	Genentech	2005-present

Research Interests:

Primary research focuses on the inflammatory and autoimmune mechanisms. Currently, in biotechnology working on the development of new biological therapeutic agents for immunologic and inflammatory respiratory and other Th2 diseases. Current work includes the design of mechanism of action studies, selection of useful pharmacodynamic endpoints, diagnostic markers and study of surrogate efficacy measures as well as elucidating new biology, while performing concise, informative trials and conduct of proof-of-concept studies. In the past, study of immunologic and inflammatory processes in allergic and lung diseases, and identification of modulators of the human allergic inflammatory process.

Research:

- The effect of the Cockroach protein Lipophorin on Asthma.
  Duke University Medical Center, Durham, NC.

- A Randomized, Double-Blind, Multicenter, Repeat Dosing, Cross-Over Trial Comparing the Safety, Pharmacokinetics, and Clinical Outcomes of IGIV-Chromatography, 10% (Experimental) with IGIV-Solvent Detergent Treated, 10% (Control) in Patients with Primary Humoral Immunodeficiency.
  Duke University Medical Center and Bayer Pharmaceutical Division.

CHAPTER REVIEWS, MANUSCRIPTS AND ABSTRACTS:

Raymond G. Slavin, MD; Tmirah Haselkorn, PhD; June H. Lee, MD; Beiyao Zheng, PhD; **Yamo Deniz, MD**; and Sally E. Wenzel, MD for the TENOR Study Group: Asthma in older adults: observations from theEpidemiology and Natural History of Asthma:Outcomes and Treatment Regimens (TENOR) study. *Ann Allergy Asthma Immunol.* 2006;96:406–414.

Chipps B, MD, Szefler S, MD, Lee J, MD, Haselkorn T, PhD, Mink D, MS, **Deniz Y, MD**, and Simons E, MD for the TENOR Study Group: Demographic and Clinical Characteristics of Children and Adolescents with Severe or Difficult-to-Treat Asthma (*In Print, J Allergy and Clinical Immunology)*

Thomas B Casale, MD; William W Busse, MD; Joel N Kline, MD; Zuhair K Ballas, MD; Mark H Moss, MD; Robert G Townley, MD; Masoud Mokhtarani, MD; Vicki Seyfert-Margolis, PhD; Adam
Asare, PhD; Kirk Bateman; **Yamo Deniz, MD** and the Immune Tolerance Network Group: Omalizumab pretreatment decreases acute reactions following rush immunotherapy for ragweed-induced seasonal allergic rhinitis. *J Allergy and Clinical Immunol. 2005 Jan; 117(1): 135-140*

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Stephen Holgate, MD, Thomas Casale, MD, Sally Wenzel, MD, Jean Bousquet, MD, **Yamo Deniz, MD**, and Colin Reisner, MD: Anti-inflammatory effects of Omalizumab confirm central role of IgE in allergic inflammation. *J Allergy Clin Immunol. 2005 Mar; 115(3):459-65.*

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Jonathan Corren, MD, Thomas Casale, MD, **Yamo Deniz, MD**, and Mark Ashby, PhD: Omalizumab, a recombinant humanized anti-IgE antibody, reduces asthma-related emergency room visits and hospitalizations in patients with allergic asthma. *J Allergy Clin Immunol 2003; 111:87-90*

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J. Corren, S. Hedgecock, G. Ayre, Y. Deniz: Omalizumab is effective in reducing asthma exacerbations irrespective of concomitant long-acting beta2-agonist use. J Allergy Clin Immunol. 113:(2) S36. 2004

B. Chipps, K. Kim, P. Korenblat, **Y. Deniz**, B. Zheng, A. Carroll: Effect of Omalizumab on Healthcare Utilization in Patients with Moderate to Severe Allergic Asthma. *J Allergy Clin Immunol. 111(2): S144.* 2003

Guenther Hochhaus, PhD; Laurence Brookman, PhD; Howard Fox, MD; Charles Johnson, MD; John Matthews, MD; Song Ren, PhD; and **Yamo Deniz, MD**: Pharmacodynamics of omalizumab: implications for clinical efficacy and dosing in the treatment of allergic asthma. *Current Medical Research and Opinion July 21, 2003.*

L Borish, C M Dolan, **Y Deniz**, B Zheng. Epidemiology of total serum IgE in a large clinical cohort of subjects with severe or difficult to treat asthma. *European Respiratory Journal* 20(38):513s (P3200). 2002

Wenzel S, Dolan C, **Deniz Y**, Zheng B, and Weiss S: Barriers to asthma control are associated with future health care utilization in patients with severe or difficult-to-treat asthma. *J Allergy Clin Immunol. 111(2):S107. 2003*

Wenzel S, Dolan CM, Borish L, Chipps B, Cohen T, **Deniz Y**, Hayden ML, Weiss S, Bleecker E: NAEPP Guideline-based Assessment of Asthma Underestimates Severity Compared with Physician Assessment in a Large Cohort of Patients with Severe or Difficult-to-Treat Asthma. *(Submitted to American Journal of Critical Care Medicine).*

Stodberg T, **Deniz Y**, Esteite N, Jacobsson B, Dahl H, Zweygberg Wirgart B, Grillner L, Linde A: A case of Diffuse Leptomeningeal Oligodendrogliomatosis Associated with HHV-6 Variant A. *Neuropediatrics 2002; 33: 266-270*

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Fink MP, Rothschild HR, **Deniz Y**, Cohn SM: Complement depletion with Naje Haje cobra venom factor limits prostaglandin release and improves visceral perfusion in porcine endotoxic shock *Journal of Trauma. 29 (8): 1076-84*, 1989

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Effect of Ibuprofen and Meclofenamate. *Journal of Applied Physiology. 67 (5):1950-57, 1989*

Fink MP, Cohn SM, Lee PC, **Deniz Y**, Wang H, Fiddian-Green RG: Effect of lipopolysaccharide on intestinal intramucosal hydrogen ion concentration in pigs: evidence of gut ischemia in a normodynamic
model of septic shock. *Critical Care Medicine. 17 (7): 641-46, 1989*

Massanari M, **Deniz Y**, Maykut R, Reisner C, Geba G: Omalizumab improves asthma outcomes irrespective of leukotriene receptor antagonist use. Poster Presentation at Federation for Clinical Immunology Societies 2005.

Maykut RJ, **Deniz Y**, Massanari M, Reisner C, Kianifard, F, Geba GP: Response of older patients with asthma to omalizumab: A pooled analysis across five clinical trials. Poster Presentation at Federation for Clinical Immunology Societies 2005.

Massanari M, **Deniz Y**, Lee J, Kianifard F, Blogg M, Reisner C, Geba G: Omalizumab improves asthma control and reduces rescue steroid bursts in patients with moderate-to-severe allergic asthma. Poster Presentation at ATS 2005.

T. Haselkorn, C. Dolan, D. Wong D. Miller, **Y. Deniz** L. Borish: High prevalence of skin test positivity in patients with severe or difficult-to-treat asthma. Poster Presentation at AAAAI 2004.

L Borish, C M Dolan, **Y Deniz**, B Zheng: Epidemiology of total serum IgE in a large clinical cohort of subjects with severe or difficult to treat asthma. Poster Presentation at ERS 2004.

Sally Wenzel, MD, Eugene Bleecker, MD, Mary K Miller, MS, Michelle Pritchard, MS, Dave Miller, ABD and **Yamo Deniz, MD**: Lack of agreement between GINA guidelines and physician assessment of asthma severity. Poster Presentation at ERS 2004.

S Wenzel, MD, M K Miller, L Borish, MD, B Zheng, PhD, E H Warren and Y Deniz, MD: Combination asthma medication and healthcare use in severe or difficult-to-treat asthma. Poster Presentation at ERS 2004.

K. Mascia, **T.** Haselkorn, **Y. Deniz,** M. Mangeshkar, **E.** Bleecker, L. Borish: Aspirin intolerance and severity of asthma: Evidence for remodeling in a cohort of severe asthmatics. Poster Presentation at ACAAI 2004.

T. Haselkorn, C. Dolan, D. Miller, **Y. Deniz**, L. Borish, D. Wong: High prevalence of skin test positivity in patients with severe or difficult-to-treat asthma. Poster Presentation at ACAAI 2004.

Bresnahan B, Wenzel S, Dolan **C, Deniz Y**, Zheng **B**, and Weiss S for the TENOR Study Group: Barriers to asthma control are associated with future health care utilization in patients with severe or difficult-to-treat asthma. Poster presentation at IHEA 2003.

L Borish, C M Dolan, **Y Deniz**, E Warren, B Zheng: Elevated total serum IgE in a large clinical cohort of subjects with severe or difficult-to-treat asthma. Poster presentation at ATS 2003

Bleecker E, Bresnahan B, Hayden ML, Warren E, **Deniz Y:** Asthma-related Quality of Life in Patients with Severe or Difficult-to-Treat Asthma. Poster presentation at ATS 2003.

Hayden ML, Johnson CA, **Deniz Y**, Dolan CM, Bleecker ER: High Level Health Care Utilization in Severe and Difficult-to-treat Asthma. Poster presentation at AMCP 2002

MEMBERSHIP IN SOCIETIES:

- Fellow, American Academy of Asthma Allergy and Immunology
- Member, American College of Allergy Asthma and Immunology
- Member, Joint Council of Allergy, Asthma and Immunology
- Member, American Thoracic Society
- Member, American Medical Association
- Member, American Academy of Pediatrics
- Swedish Medical Association
- Swedish Pediatric Allergy Society
- Member, American Association of Clinical Anatomists
- Member, Massachusetts Medical Society
- Member, Worcester District Medical Association
- Member, American Chemical Society

GRAND ROUNDS AND DEPARTMENTAL SEMINARS (by invitation):

09/2002	Karolinska Institute Hospital Astrid Lindgren Children's Hospital Department of Pediatrics Stockholm, Sweden
04/2003	Scripps Institute Medical Center Department of Pediatrics La Jolla, CA
04/2003	San Diego Allergy Society San Diego, CA
04/2003	Duke University Medical Center Div. of Pediatric Allergy and Immunology Durham, NC
04/2003	Wake Forest University Medical Center Div. of Pulmonary Medicine Wake Forest, NC
05/2003	Eastern Allergy Society West Palm Beach, FL
08/2003	New York University Medical Center Div. of Pulmonary Medicine New York, NY
02/2004	Stanford University Division of Pulmonary Medicine Palo Alto, CA

10/2004 Brigham and Women Hospital
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ADMINISTRATIVE MERITS:

- Founder, International Suryoye Medical Association (1996)
- President, International Suryoye Medical Association (1996-2001)
- President, North America Assyrian Youth Organization (1987-1991)
- Soccer Coach (1983-1997)
- Student Program for Urban Development (1984-1987).

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